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Moving Muscle: Jeb Signaling in *Drosophila*

A recent study identifies a novel nonautonomous signaling pathway that regulates cell migration and differentiation in early *Drosophila* mesodermal tissues.

Drosophila mesoderm originates from the ventral-most cells in the early embryo; these cells invaginate at gastrulation and form a monolayer of cells running the length of the embryo. Subsequently, the mesoderm is subdivided into distinct subtypes (somatic body wall muscles, visceral muscles, heart muscles, and the fat body). Somatic mesoderm is specified as a nearly continuous group of cells running the length of the embryo, whereas visceral mesoderm first appears as discrete clusters of cells in each segment (Figure 1A). One of the most striking features of mesoderm morphogenesis is the dramatic and directed migrations performed by these pools of developing mesodermal cells. For example, the initial clusters of visceral mesodermal cells show two directed migrations: first they spread to form a continuous band of cells along the length of the embryo (moving parallel to the somatic mesoderm), and, subsequently, they migrate into the embryo to fully ensheath the intestinal tract.

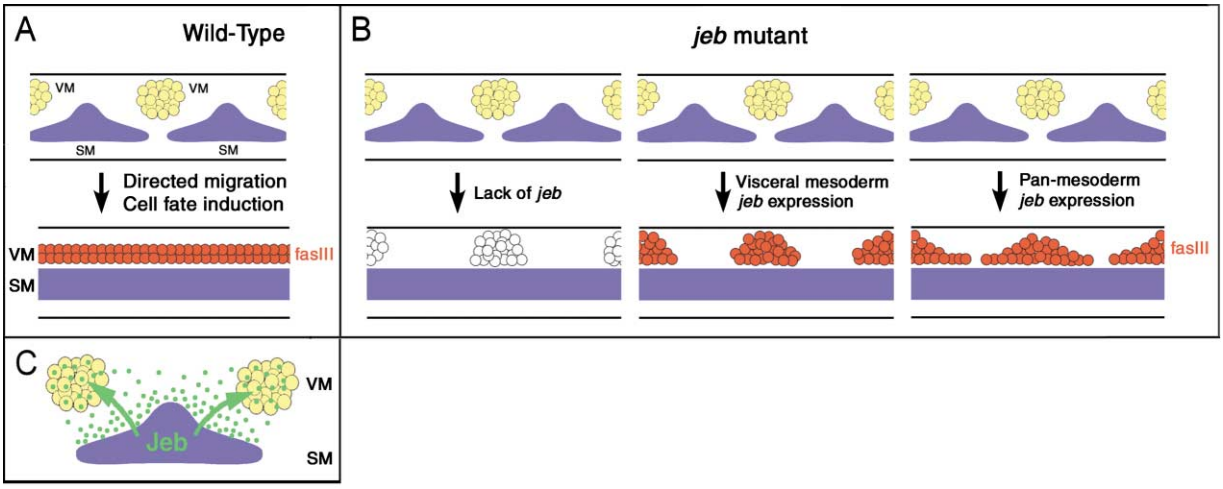
A growing number of transcription factors are known to specify the fate of each type of mesoderm. At the top of the hierarchy is the bHLH transcription factor *twist*, which is required for all mesodermal cell fates and activates transcription factors such as *bagpipe* (*bap*) and *tinman* (*tin*) that are required for specific mesodermal subtypes. *bap* is essential to make visceral mesoderm, and *tin* is required for the formation of both visceral mesoderm and heart muscle. Mammalian homologs of these genes have been identified and their roles in mesoderm development appear to be well conserved (Furlong et al., 2001, and references therein). We know little, however, about the transcriptional targets of these mesodermal genes and even less about the coordinated regulation of gene expression, cell migration, and differentiation that occurs during the later steps of mesoderm development. It is this unexplored area that Weiss et al. (2001, November 2 issue) have begun to illuminate, in a recent issue of *Cell*, by screening for transcriptional targets of the *tin* gene.

tin is expressed early in all mesoderm, but later its expression is restricted to the precursors of visceral and heart mesoderm; these tissues are missing in *tin* mutants, making *tin* a tantalizing candidate for specifying visceral and heart musculature. To identify *tin* target genes, Weiss et al. screened a library consisting of short fragments of *Drosophila* genomic DNA cloned in front of a reporter construct and identified clones that would direct reporter gene activation in a *tin*-dependent fashion. They isolated a small number of fragments, including one that maps adjacent to the *jelly-belly* (*jeb*) locus. Weiss et al. generated *jeb* mutants and observed that in these mutants visceral mesoderm precursors form normally as discrete clusters in each segment but then fail to migrate and fail to express certain differentiation markers. In contrast, somatic muscle and fat body appear to form normally in *jeb* mutants. Thus, a major portion of visceral mesoderm induction requires *jeb*.

Interestingly, the *jeb* gene is not expressed in the developing visceral mesoderm, but in the flanking somatic mesoderm precursors, which are closely associated with the visceral mesoderm and may in fact be the substrate for the first visceral mesoderm migration. This domain overlaps with the earliest expression of *tin*, leaving open the possibility that *jeb* is a true transcriptional target of *tin*, though other factors likely play a redundant role as *jeb* expression is unchanged in the absence of *tin* function. *jeb* encodes a small protein with a predicted secretory signal and a single LDL receptor-repeat domain and appears to be secreted: *jeb* is transcribed only in the somatic mesoderm, but Jeb protein can be detected within the visceral mesoderm. Weiss et al. suggest that the Jeb protein is secreted from the somatic mesoderm and taken up by the visceral mesoderm. Additional evidence for this secretion model is as follows: (1) expression of *jeb* in tissue culture cells results in the majority of Jeb protein detected in the culture medium; (2) removal of the LDL receptor-repeat domain of Jeb blocks uptake of Jeb by the visceral mesoderm; and (3) genetic blockade of receptor-mediated endocytosis abolishes Jeb staining in visceral mesoderm but not in somatic mesoderm. Taken together, these data provide compelling evidence that Jeb is secreted by somatic mesoderm, taken up by neighboring visceral mesoderm, and required to induce the directed migration and differentiation of visceral mesoderm.

The location of the Jeb signal appears to be critical for directing visceral mesoderm migration but not differentiation. When *jeb* mutants are resupplied with *jeb* expression just in the visceral mesoderm, differentiation occurs normally, but proper migration is not observed (the cells remain "clumped"). Similarly, when *jeb* is expressed in both visceral and somatic mesoderm, there is rescue of visceral mesoderm differentiation, but migration remains abnormal (Figure 1B); this is true even when the embryo contains a wild-type *jeb* gene. One missing piece of data (because the appropriate reagents are not yet available) is the demonstration that somatic mesoderm-specific expression of *jeb* fully rescues both defects. The simplest model is that Jeb signals from the somatic mesoderm to direct visceral mesoderm migration and differentiation (Figure 1C), with proper migration requiring restriction of *jeb* expression to the somatic mesoderm. If this is indeed the case, it would provide an interesting example of how one signal coordinates both cell fate induction and cell migration.

How is the Jeb signal transduced? Extracellular Jeb protein appears to be taken up by visceral mesoderm but not other nearby tissues (e.g., epithelia), suggesting the existence of a visceral mesoderm-specific receptor for Jeb. A number of LDL receptor repeat-containing proteins have been described, but many of these have transmembrane domains and act as receptors themselves, signaling in a cell-autonomous fashion (Cooper and Howell, 1999).



Jeb Drives Visceral Mesoderm Migration and Fate Specification

(A) Morphogenesis of somatic and visceral mesoderm in wild-type embryos. Two segments are diagrammed. Visceral (yellow) and somatic (blue) mesodermal precursors are segregated from the mesoderm primordium. Visceral mesoderm precursors first appear as discrete clusters of cells in each segment. Next they migrate along the AP axis to form a continuous group of cells and express the visceral mesoderm differentiation marker FasIII (red).

(B) In *jeb* mutants, visceral mesoderm cells fail to migrate or strongly express FasIII. Misexpression of jeb in visceral mesoderm, or throughout mesoderm, fully rescues differentiation but not migration.

(C) Jeb protein (green) is proposed to be secreted from somatic mesoderm and specifically taken up by visceral mesoderm, thereby directing its migration and inducing differentiation.

A limited number are thought to signal in a non-cell-autonomous fashion as proposed for Jeb (Hong and Hashimoto, 1995; Sym et al., 1999), but only one is known to be secreted (Li et al., 2000), and how these molecules accomplish signal transduction remains enigmatic. Further studies of *jeb* function will certainly shed light on this novel type of signaling pathway, as well as its role in other tissues: Weiss et al. show that *jeb* is also robustly expressed in a small subset of axons in the embryonic CNS and that this localization depends upon its LDL receptor repeat domain. It will be exciting to see if Jeb is in fact required for both brains and brawn.

Marc R. Freeman and Chris Q. Doe
Institutes of Neuroscience
and Molecular Biology/HHMI
University of Oregon
Eugene, Oregon 97403

Selected Reading

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How the Brain Sees Smells

Genetically encoded transneuronal tracers provide the first glimpse into the logic of olfactory processing in higher cortical areas of the brain. The results suggest a complex distributed coding scheme, which is remarkably similar in different individuals.

Honeysuckle. Vinegar. Chocolate. Jasmine. Conscious perception of these and thousands of other odors is made possible by the olfactory system, which has the remarkable power to detect complex blends of odors in the environment and transform them into meaningful neural representations.

How does the olfactory system parse the complex and contradictory blend of scents that animals encounter daily in their natural environment? Ten years ago, Linda Buck and Richard Axel provided a simple and elegant answer to the problem of olfactory recognition (Buck and Axel, 1991). They identified a novel and extremely large family of genes encoding up to 1000 different G protein-coupled receptors selectively expressed in olfactory sensory neurons (Buck and Axel, 1991; Ressler et al., 1993; Vassar et al., 1993). These candidate odorant receptors bind odorous ligands and activate a cAMP-mediated second messenger cascade that results in the propagation of odorant-specific synaptic activity in the brain. The thousands of neurons that express a given odorant receptor, and therefore responsive to the same odors, are scattered throughout the olfactory epithelium of the nose. However, in a remarkable feat of precise axon guidance, all the axons